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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

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12/14/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,127	CAMPOCHIARO ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7,8,22,27,31,36,40 and 49* is/are pending in the application.

4a) Of the above claim(s) *7,8 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,27,31,36,40 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/15/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 2 September 2009.

Claim Status

Claims 1-3, 7, 8, 22, 27, 31, 36, 40 and 49 are pending. Claims 4-6, 9-21, 23-26, 28-30, 32-35, 37-39 and 41-48 are cancelled. The applicant has indicated that claims 1-3, 27, 31, 36, 40 and 49 read on the elected species. However, claims 7, 8 and 22 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1-3, 7, 27, 31, 36, 40 and 49 are under current examination.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 15 March 2009 consisting of 2 sheet(s) are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

Priority

This application claims benefit under 35 USC 371 as a National Stage entry of PCT/EP03/09497 (filed 27 August 2003). This application also claims benefit from provisional U.S. Application No. 60/406,470, filed 28 August 2002. The instant application has been granted the benefit date, 28 August 2002, from the application 60/406,470.

RESPONSE TO ARGUMENTS

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10/080797

Claims 1-3, 27, 31, 36, and 42 remain provisionally rejected on the ground of nonstatutory double patenting over claims 1-3, 27-28, 30-32, 38-41, 45, 51-62 of copending Application No. 10/080797 for the reasons of record and the comments below.

The applicant's arguments have been fully considered but are unpersuasive.

The applicant argues that he will "consider filing a Terminal Disclaimer on indication of otherwise allowable subject matter" (Remarks, filed 9/2/2009, page 4). The examiner acknowledges this comment. However, because the claims of the co-pending applications appear to still be obvious over each other, the examiner finds this argument unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 1-3, 27, 31, 36, and 42 remain provisionally rejected on the ground of nonstatutory double patenting over claims 1-3, 27-28, 30-32, 38-41, 45, 51-62 of copending Application No. 10/080797.

The examiner reiterates the pending rejection:

Claims 1-3, 27, 31, 36, and 42 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-3, 27-28, 30-32, 38-41, 45, 51-62 of copending Application No. 10/080797. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that

copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The instant application is directed to treating retinal edema, while the copending application, 10/080797, is directed to treating a large genus of diseases for which retinal edema is a symptom. Both applications use gene therapy methods to deliver the same SEQ ID NO encoding human endostatin. Accordingly, the claims of 10/080797 are obvious over the instant claims.

10/529428

The examiner withdraws the rejection of claims 1-3, 31, and 36 provisionally rejected on the ground of nonstatutory double patenting over claims 1-4, 9, 11, 16 of copending Application No. 10/529428 because the instant application is now directed to methods using subretinal injection while the copending application is directed to periocular injection.

10/910293

Claims 1 and 31 remain provisionally rejected on the ground of nonstatutory double patenting over claims 52-56, and 59 of copending Application No. 10/910293 for the reasons of record and the comments below.

The applicant's arguments have been fully considered but are unpersuasive.

The applicant argues that he will “consider filing a Terminal Disclaimer on indication of otherwise allowable subject matter” (Remarks, filed 9/2/2009, page 4). The

examiner acknowledges this comment. However, because the claims of the co-pending applications appear to still be obvious over each other, the examiner finds this argument unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 1 and 31 remain provisionally rejected on the ground of nonstatutory double patenting over claims 52-56, and 59 of copending Application No. 10/910293.

The examiner reiterates the pending rejection:

Claims 1 and 31 are provisionally rejected on the ground of nonstatutory double patenting over claims 52-56, and 59 of copending Application No. 10/910293. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The instant application is directed to treating retinal edema, while the copending application, 10/910293, is directed to treating the retina of a subject in need of such delivery encompassing a large genus of diseases for which retinal edema is a symptom. Both applications use gene therapy methods to deliver nucleic acids encoding human endostatin. The claims of Application 10/910293 are more generic than those of the instant application, however, the claims of 10/910293 recite Markush groups which encompass the specific embodiment of the instant claims directed to methods of treating retinal edema with a

lentivirus encoding endostatin. As the specification of 10/910293 teaches that subretinal injection is a species of their delivery methods, the claims of 10/910293 are obvious over the instant claims.

35 USC § 112, 2nd paragraph

The rejection of claims 1-3, 5, and 33 under 35 USC 112, 2nd paragraph is withdrawn in response to the applicant's arguments and/or claim amendments. The applicant's arguments have been fully considered and are persuasive. The applicant has amended the claim1 so that the "missing element" (i.e., viral vector comprising an endostatin-encoding nucleic acid) has been added to the claim. Dependent claims 2-3 are thereby rectified. There is perfect clarity regarding this word usage. Claims 5 and 33 have been cancelled; therefore, the rejection of these claims is moot. Therefore, the examiner hereby withdraws the rejection of claims 1-3, 5, and 33 under 35 USC 112, 2nd paragraph.

35 USC § 102

Leboulch

The rejection of claims 1-3 and 27 under 35 U.S.C. 102(b) as being anticipated by Leboulch et al (WO99/26480) and as evidenced by Chu et al. (Drug Development Research. 2008; 69:1-14) is withdrawn due to the applicant's claim amendments and arguments. The applicant's arguments and claim amendments have been fully considered and are persuasive. The applicant has submitted claim amendments which

introduced the limitation, "subretinal injection" into claim 1. This limitation is not taught by Leboulch. Therefore, the examiner hereby withdraws the rejection of claims 1-3 and 27 under 35 U.S.C. 102(b) as being anticipated by Leboulch et al and as evidenced by Chu et al.

Mori

The rejection of claims 1, 5, 6 under 35 U.S.C. 102(a) as being anticipated by Mori et al. (American Journal of Pathology. July 2001; 159(1): 313-320) is withdrawn due to the applicant's claim amendments and arguments.

The applicant's arguments and claim amendments have been fully considered and are persuasive.

The applicant has submitted claim amendments which introduced the limitation, "subretinal injection" into claim 1. This limitation is not taught by Mori.

Therefore, the examiner hereby withdraws the rejection of claims 1, 5, 6 under 35 U.S.C. 102(a) as being anticipated by Mori et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Leboulch & Poeschla

The rejection of claims 1, 5, 6, 31, 36 and 37 under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al (WO99/26480) in view of Poeschla et al. (US-6,555,107) is withdrawn in response to the applicant's claim amendments and/or arguments.

The applicant's arguments and claim amendments have been fully considered and are persuasive.

The applicant has submitted claim amendments which introduced the limitation, "subretinal injection" into claim 1. This limitation is not taught by Leboulch or Poeschla.

Therefore, the examiner hereby withdraws the rejection of claims 1, 5, 6, 31, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al in view of Poeschla et al.

Leboulch, Poeschla & Clark

The rejection of claims 41-42 under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al (WO99/26480) in view of Poeschla et al. (US-6,555,107) as applied to claims 1, 5, 6, 31, and 36 above, and further in view of Clark et al. (Exp. Opin. Ther. Patents. 2000; 10(4): 428-448) is withdrawn in response to the applicant's claim amendments and/or arguments.

The applicant has cancelled claims 41-42. Therefore, the rejection of these claims is moot.

Accordingly, the examiner hereby withdraws the rejection of claims 41-42 under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al in view of Poeschla et al. as applied to claims 1, 5, 6, 31, and 36 above, and further in view of Clark et al.

Leboulch, Poeschla & Mori

The rejection of claims 32-35 under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al (WO99/26480) in view of Poeschla et al. (US-6,555,107) as applied to

claims 1, 5, 6, 31, and 36 above, and further in view of Mori et al. (American Journal of Pathology. July 2001; 159(1): 313-320) is withdrawn in response to the applicant's claim amendments and/or arguments.

The applicant has cancelled claims 32-35. Therefore, the rejection of these claims is moot.

Accordingly, the examiner hereby withdraws the rejection of claims 32-35 under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al. in view of Poeschla et al. as applied to claims 1, 5, 6, 31, and 36 above, and further in view of Mori et al.

Leboulch, Poeschla & Brandt

Claims 1, 31, 36 and 40 remain rejected under 35 U.S.C. 103(a) as being obvious over Leboulch et al (WO99/26480) in view of Poeschla et al. (US-6,555,107) and further in view of Brandt et al. (US-6106826) for the reasons of record and the comments below.

The applicant's arguments have been fully considered but are unpersuasive.

The applicant has amended claim 1 to incorporate limitations that the viral vector comprises an endostatin-encoding nucleic acid and is delivered by subretinal injection. These limitations are taught by at least one of the cited references.

The applicant argues neither Leboulch nor Poeschla teach subretinal injection. The examiner concedes that neither Leboulch nor Poeschla teach subretinal injection. The applicant concedes that Brandt et al. teaches the phrase, "subretinal injection," but

argues that the references to this method of delivery do not support the claimed invention. In particular, the applicant points out that one of the two references to "subretinal injection," refers to successful labeling of retinal cells by subretinal injection of viral vectors encoding genes encoding labels (e.g., lacZ). This demonstrates that following subretinal injection of viral vectors, retinal cells are capable of uptake of genes and expression of the encoded protein. In the examiner's view, this method demonstrated the predictability of subretinal injection methods for administration of genes to retinal cells. However, the applicant interprets Brandt's subsequent teachings that "[s]o far, researchers have only been able to 'label' retinal cells via subretinal injection, which causes retinal detachment in the area of the injection" (Brandt, col.4, lines 8-9) as teaching away from the claimed method of treating retinal edema. Despite these contrary indications of usefulness for subretinal injection in gene therapy methods, Brandt teaches that "subretinal or intravitreal injection of a number of growth factors, cytokines and neurotrophins...have been shown to restore specific function to retinal or retinal pigment epithelial cells" (col.8, lines 29-32). Brandt further teaches "recombinant HSV vectors that express growth factors, cytokines and neurotrophins are suitable for treating ocular neuronal degenerative diseases and disorders, including…macular degeneration" (col.8, lines 57-60). As the "wet" form of macular degeneration results from retinal edema and has the symptom of retinal detachment, a skilled artisan would not be concerned with the ambiguity of retinal detachment when trying to treat retinal edema in patients with macular degeneration. The skilled artisan would be more focused on inhibiting the growth of blood vessels when administering

therapeutic genes by subretinal injection. A skilled artisan in the possession of Brandt would consider the successful use of subretinal injection for (1) delivery of therapeutic proteins for treating macular degeneration and (2) genes encoding labels and (3) Brandt's suggestion to deliver therapeutic genes for treating macular degeneration as a suggestion by Brandt that therapeutic genes could be successfully delivered by subretinal injection to treat retinal edema. Accordingly, the examiner finds the applicant's argument unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 1-7 and 16-18 remain rejected under 35 U.S.C. 103(a) as being obvious over Leboulch et al. in view of Poeschla et al. and further in view of Brandt et al.

The examiner reiterates the reworded, pending rejection below:

Claims 1, 31, 36 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al (WO99/26480) in view of Poeschla et al. (US-6,555,107) and further in view of Brandt et al. (US-6106826)

Claim 1 is directed to a method for the treatment of retinal edema in an individual afflicted with retinal edema, comprising effecting an increase in the amount of endostatin in ocular tissues of an individual afflicted with retinal edema to a retinal edema-inhibiting effective amount, wherein the increase is effected by a subretinal injection of an effective amount of a viral vector comprising an endostatin-encoding nucleic acid to the individual.

Leboulch et al. teach a method of treating a human patient suffering from diabetic retinopathy comprising administering a nucleic acid molecule which expresses the anti-

angiogenic polypeptide endostatin, wherein expression of endostatin in the patient inhibits angiogenesis in the vicinity of the retina (claim 33). A skilled artisan is aware that diabetic retinopathy is characterized by neovasculaturization of the retina resulting in retinal edema. So, while treating diabetic retinopathy with nucleic acids encoding endostatin, Leboulch et al. are treating retinal edema. Regarding the limitations directed to "to a retinal edema-inhibiting effective amount," the specification does not specifically define this phrase. However, the specification provides a definition for to a "retinal disorder inhibiting effective amount" and indicates that this amount is determined by observation of endostatin's effect on retinal vascular permeability, retinal thickness or degree of retinal detachment. The specification also indicates "[a] therapeutically effective dose of an active agent can be estimated either in cell culture assays…or in animal models" (page 7, parag.5). The claimed amount is not quantitatively exact, but is determined empirically. Therefore, the examiner concludes that Leboulch et al. provides such an amount. Regarding the limitation "wherein the increase is effected by causing endostatin to be produced within an individual," Leboulch et al teach gene therapy methods in humans. Regarding the limitation, "wherein the increase is effected by administering an effective amount of a viral vector comprising and endostatin-encoding nucleic acid to the individual," Leboulch et al. teach "the nucleic acid molecule preferably constitutes a portion of a viral vector, which can...[be] administered to the patient so that...cells are infected" (page 2, lines 14-18).

In summary, Leboulch et al. teach a method of treating a human patient suffering from diabetic retinopathy comprising administering a nucleic acid molecule which

expresses the anti-angiogenic polypeptide endostatin, wherein expression of endostatin in the patient inhibits angiogenesis in the vicinity of the retina. A skilled artisan is aware that diabetic retinopathy is characterized by neovasculaturization of the retina resulting in retinal edema. So, while treating diabetic retinopathy with nucleic acids encoding endostatin, Leboulch et al. are treating retinal edema.

Leboulch et al. does not teach using lentiviral vectors, and particularly Bovine Immunodeficiency Virus (BIV) vectors, in their method of treating retinal edema with nucleic acids encoding human endostatin. Furthermore, Leboulch does not teach subretinal injection of viral vectors.

However, Poeschla et al teach non-primate lentivirus vectors, including Bovine Immunodeficiency Virus (BIV) vectors are "potential sources of safer lentiviral vectors…for therapeutic gene transfer" (col.2, lines 10-34). In addition, Poeschla et al teach methods of gene therapy comprising infecting a cell of the eye with a non-primate lentivirus capable of expressing a heterologous gene (col.33, line 6). Furthermore, Poeschla et al. teach methods of administration comprising injection.

Poeschla et al. do not teach subretinal injection of viral vectors.

Brandt et al. teach method of gene therapy for treating retinal diseases (abstract). Brandt et al. teach subretinal injection of polypeptides for treatment of ocular diseases (col.8, line 29) and suggest that recombinant viral vectors that express said polypeptides would be useful for treating ocular disease (col.8, line 52). Accordingly, a skilled artisan would be guided by Brandt to administer viral vectors by subretinal injection to treat retinal diseases with gene therapy methods.

Brandt et al. twice teaches the phrase, "subretinal injection." One of the two references to "subretinal injection," refers to successful labeling of retinal cells by subretinal injection of viral vectors encoding genes encoding labels (e.g., lacZ). This demonstrates that following subretinal injection of viral vectors, retinal cells are capable of uptake of genes and expression of the encoded protein. In the examiner's view, this method demonstrated the predictability of subretinal injection methods for administration of genes to retinal cells. However, Brandt's subsequent teachings that "[s]o far, researchers have only been able to 'label' retinal cells via subretinal injection, which causes retinal detachment in the area of the injection" (Brandt, col.4, lines 8-9) could be viewed as teaching away from the claimed method of treating retinal edema. Despite these contrary indications of usefulness for subretinal injection in gene therapy methods, Brandt teaches that "subretinal or intravitreal injection of a number of growth factors, cytokines and neurotrophins...have been shown to restore specific function to retinal or retinal pigment epithelial cells" (col.8, lines 29-32). Brandt further teaches "recombinant HSV vectors that express growth factors, cytokines and neurotrophins are suitable for treating ocular neuronal degenerative diseases and disorders, including…macular degeneration" (col.8, lines 57-60). As the "wet" form of macular degeneration results from retinal edema and has the symptom of retinal detachment, a skilled artisan would not be concerned with the ambiguity of retinal detachment when trying to treat retinal edema in patients with macular degeneration. The skilled artisan would be more focused on inhibiting the growth of blood vessels when administering therapeutic genes by subretinal injection. A skilled artisan in the possession of Brandt

would consider the successful use of subretinal injection for (1) delivery of therapeutic proteins for treating macular degeneration and (2) genes encoding labels and (3) Brandt's suggestion to deliver therapeutic genes for treating macular degeneration as a suggestion by Brandt that therapeutic genes could be successfully delivered by subretinal injection to treat retinal edema.

Claim 31 is directed to the method of claim 1, wherein the viral vector is a lentiviral vector. Poeschla et al teach non-primate lentivirus vectors, including Bovine Immunodeficiency Virus (BIV) vectors are "potential sources of safer lentiviral vectors…for therapeutic gene transfer" (col.2, lines 10-34).

Claim 36 is directed to the method of claim 31, wherein the lentiviral vector is a bovine immunodeficiency viral (BIV) vector. Poeschla et al teach non-primate lentivirus vectors, including Bovine Immunodeficiency Virus (BIV) vectors are "potential sources of safer lentiviral vectors…for therapeutic gene transfer" (col.2, lines 10-34).

Claim 40 is directed to the method of claim 1, wherein the increase is inducibly effected by the administration to the individual of a viral vector that can cause the production in the individual of an agent that will induce the expression of the endostatin-encoding nucleic acid. Brandt et al. suggest gene therapy methods of treating retinal diseases comprising viral vectors having inducible promoters operably linked to a therapeutic gene (abstract and col.2, line 56).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Leboulch et al. and Poeschla et al. and Brandt et al. to treat retinal edema using lentiviral vectors such as Bovine

Immunodeficiency Virus (BIV) comprising the gene for human endostatin, using delivery methods including subretinal injection. Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (gene therapy methods comprising administering the human endostatin gene for treating retinal edema, gene therapy methods comprising a BIV delivery vector, and subretinal injection) are taught by Leboulch or Poeschla or Brandt and further they are taught in various combinations and are shown to be used in gene therapy methods for the eye. It would be therefore predictably obvious to use a combination of these elements in a method of gene therapy for retinal edema.

The person of ordinary skill in the art would have been motivated to make those modifications because Poeschla et al teach non-primate lentivirus vectors, including BIV, are "potential sources of safer lentiviral vectors…for therapeutic gene transfer" (col.2, lines 10-34). In addition, subretinal injections were known in the art of treating retinal diseases.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Leboulch et al. and Poeschla et al. and Brandt et al. because the cited art provides examples of successful gene delivery by subretinal and intravitreal injection.

Therefore the method as taught by Leboulch et al in view of Poeschla et al. and further in view of Brandt et al. would have been *prima facie* obvious over the method of the instant application.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not

commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Rasmussen

Claims 1-3, 27, 31 and 49 are rejected under 35 U.S.C. 103(a) as being obvious over Rasmussen et al. (Drug Discovery Today. 22 November 2001; 6(20): 1171-1175).

Claim 1 is directed to a method for the treatment of retinal edema in an individual afflicted with retinal edema, comprising effecting an increase in the amount of endostatin in ocular tissues of an individual afflicted with retinal edema to a retinal edema-inhibiting effective amount, wherein the increase is effected by a subretinal injection of an effective amount of a viral vector comprising an endostatin-encoding nucleic acid to the individual. Rasmussen et al. is a review article which teaches "anti-angiogenic gene therapies for disorders of the eye" (title). Rasmussen et al. teach that macular edema (page 1171, col.2, line 22) is one of the diseases which can be treated by the methods described within the review article. Macular edema is retinal edema which occurs in the center of the retina. Furthermore, Rasmussen et al. teach that the methods of ocular gene therapy can be used to treat diabetic retinopathy, some of symptoms of which are retinal edema. Rasmussen teach gene therapy methods using recombinant viral vectors to carry the gene encoding pigment epithelium-derived factor (PEDF) or endostatin (page 1172, col.2, Anti-angiogenic gene therapy section).

Rasmussen further teaches that lentivirus (HIV) gene delivery systems can be used to delivery therapeutic proteins to the posterior part of the eye (page 1172, col.1, Gene transfer section). Additionally, Rasmussen teach that subretinal injection is of the methods of treating macular degeneration and diabetic retinopathy using gene therapy approach to deliver a viral vector which carries the gene encoding an anti-angiogenic substance (page 1174; col.1, lines 5-6; col.2, lines 6-7).

Claims 2, 3 and 27 are directed to the human endostatin polypeptide sequence of SEQ ID NO:1 (claim 2), fragments of SEQ ID NO:1 (claim 3), and the human endostatin polynucleotide sequence SEQ ID NO:2 (claim 27). The human endostatin sequence has been highly studied and is known to a skilled artisan. Furthermore, fragments of endostatin having anti-angiogenic activity are well known to a skilled artisan. Accordingly, a skilled artisan in the possession of Rasmussen would be able to utilize the claimed sequences.

Claim 31 is directed to the method of claim 1, wherein the viral vector is a lentiviral vector. Rasmussen et al teach lentivirus vectors for delivery of anti-angiogenic genes (page 1172, col.1, Gene transfer section).

Claim 49 is directed to the method of claim 1, wherein the viral vector is a retroviral vector. The lentivirus, HIV, is a retrovirus.

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to practice a method of treating retinal edema in an individual comprising subretinal injection of an effective amount of a lentiviral vector comprising an endostatin-encoding nucleic acid to the individual.

The person of ordinary skill in the art would have been motivated to practice this method, because Rasmussen teaches a gene method for treating macular edema by administering viral vectors encoding endostatin to a patient. Furthermore, Rasmussen suggests that lentivirus vectors are a suitable vector for such methods and that subretinal injection is also suitable for such treatments. Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (gene therapy methods comprising administering the human endostatin gene for treating retinal edema, gene therapy methods comprising a lentivirus delivery vectors, and subretinal injection) are taught by Rasmussen and further they are taught in various combinations and are shown to be used in gene therapy methods for the eye. It would be therefore predictably obvious to use a combination of these elements in a method of gene therapy for retinal edema.

An artisan would have expected success, because a variety of animal models have been tested with such vectors and show promise.

Therefore the method as taught by Rasmussen et al would have been *prima facie* obvious over the method of the instant application.

Rasmussen & Peoschla

Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rasmussen et al. (Drug Discovery Today. 22 November 2001; 6(20): 1171-1175). as applied to claims 1 and 31 above, and further in view of Poeschla et al. (US-6,555,107).

The teachings of claims 1 and 31 are described above in the obviousness rejection over Rasmussen.

In summary, Rasmussen suggests gene therapy methods for treating macular edema by subretinal injection of lentiviral vectors comprising endostatin.

Although Rasmussen et al. teaches using lentiviral vectors, they do not teach the particular species of lentivirus vector, Bovine Immunodeficiency Virus (BIV).

However, Poeschla et al teach non-primate lentivirus vectors, including Bovine Immunodeficiency Virus (BIV) vectors are "potential sources of safer lentiviral vectors…for therapeutic gene transfer" (col.2, lines 10-34). In addition, Poeschla et al teach methods of gene therapy comprising infecting a cell of the eye with a non-primate lentivirus capable of expressing a heterologous gene (col.33, line 6). Furthermore, Poeschla et al. teach methods of administration comprising injection.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Rasmussen et al. and Poeschla et al. to treat retinal edema using lentiviral vectors such as Bovine Immunodeficiency Virus (BIV) comprising the gene for human endostatin. Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could

have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (gene therapy methods comprising administering the human endostatin gene for treating retinal edema and gene therapy methods comprising a BIV delivery vector) are taught by Rasmussen or Poeschla and further they are taught in various combinations and are shown to be used in gene therapy methods for the eye. It would be therefore predictably obvious to use a combination of these elements in a method of gene therapy for retinal edema.

The person of ordinary skill in the art would have been motivated to make those modifications because Poeschla et al teach non-primate lentivirus vectors, including BIV, are "potential sources of safer lentiviral vectors…for therapeutic gene transfer" (col.2, lines 10-34). In addition, subretinal and intravitreal injections were know in the art of treating retinal diseases.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Rasmussen et al. and Poeschla et al. because the cited art provides examples of successful gene delivery by lentiviruses.

Therefore the method as taught by Rasmussen et al in view of Poeschla et al. would have been *prima facie* obvious over the method of the instant application.

Rasmussen & Nemerow

Claims 1-3, 27, 31, 40 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rasmussen et al. (Drug Discovery Today. 22 November 2001; 6(20): 1171-1175) in view of Nemerow et al. (US2002/0193327).

The teachings of Rasmussen are described above in the obviousness rejection over Rasmussen.

In summary, Rasmussen suggests gene therapy methods for treating macular edema by subretinal injection of lentiviral vectors comprising a nucleic acid encoding endostatin.

Rasmussen et al. does not teach using inducible promoters in their viral vectors.

Claim 40 is directed to the method of claim 1, wherein the increase is inducibly effected by the administration to the individual of a viral vector that can cause the production in the individual of an agent that will induce the expression of the endostatin-encoding nucleic acid. Nemerow et al. suggest gene therapy methods of treating retinal diseases (abstract) including macular edema (Table 4, page 15) comprising subretinal injection (parag.0024) of viral vectors having inducible promoters (parag.0060) operably linked to a therapeutic gene. Furthermore, Nemerow teaches that endostatin can inhibit angiogenesis (parag.0165).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Rasmussen et al. and Nemerow et al. to treat retinal edema by subretinal injection of a lentiviral vector comprising the gene for human endostatin operably linked to an inducible promoter.

The person of ordinary skill in the art would have been motivated to utilize inducible promoters for expression of endostatin in gene therapy methods of treating retinal edema. Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (gene therapy methods comprising administering the human endostatin gene for treating retinal edema, gene therapy methods comprising a lentivirus vector, and using inducible promoter for ocular gene therapy) are taught by Rasmussen or Nemerow and further they are taught in various combinations and are shown to be used in gene therapy methods for the eye. It would be therefore predictably obvious to use a combination of these elements in a method of gene therapy for retinal edema. In addition, in the art of gene therapy, it a desired goal to control the time and location of gene expression; inducible promoters provide control over these parameters.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Rasmussen et al. and Nemerow et al. because inducible promoters have been used successfully in gene therapy methods.

Therefore the method as taught by Rasmussen et al in view of Brandt et al. would have been *prima facie* obvious over the method of the instant application.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Scott Long/
Patent Examiner, Art Unit 1633